PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N88238 TAC/RCS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/03786	11.04.2003	16.04.2002
International Patent Classification (IPC) or both national classification and IPC		
C07D409/14		
Applicant		
ALMIRALL PRODESFARMA AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.11.2003	23.08.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03786

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-58 as originally filed

Claims, Numbers

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 30,31 (with respect to industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 31,31 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-29,32,33
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30 and 31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

For the assessment of the present claims 30 and 31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV

Lack of unity of invention

The present application **lacks unity** for the following reasons:

IV.1. According to Rule 13.1 PCT, "The International application shall relate to one invention only OR to a group of inventions so linked as to form a single general inventive concept".

This is further clarified in Rule 13.2 PCT, which details that "the requirement for unity of invention shall only be fulfilled when there is a technical relationship among those inventions involving one or more of the same corresponding special technical features that defines a contribution which each of the claimed inventions, considered as a whole makes over the prior art".

IV.2. For the purpose of unity, a single general inventive concept is required. This means that the broadest possible problem to be solved has to be drawn up (i.e. to cover all claimed possibilities). Thus by definition, the provisos may not be taken into account when determining the presence or lack of unity, since the special technical feature must define a contribution over these provisos as well.

It is considered that the problem to be solved by the present application is the provision of compounds for the treatment of gastrointestinal disorders.
The solution is provided by pyrrolidinium compounds according to the general formula (I) of claim 1.
Thus, the single general concept can be identified as the provision of pyrrolidinium compounds according to formula (I) of claim for the treatment of gastrointestinal disorders.

IV.3. The following document D1 was retrieved during the preliminary search:

D1: US-A-2 956 062 (LUNSFORD CARL D) 11 October 1960 (1960-10-11) cited in the application

D1 discloses (see compounds number 19, 24, and 31 in table I) compounds of the present formula (I) of claim 1 in which B=phenyl, n=m=0, A=-CH_2-, R_4=-CH_3, X^-=Br^-, D=i) in which R^9=phenyl, R^{10}=cyclohexyl or cyclopentyl, and R^{11}=H or OH.
The compounds of D1 are inhibitors of gastrointestinal motility.

The compounds of D1 solve the problem, namely the provision of further compounds for the treatment of gastrointestinal disorders in an identical manner to the present application. Thus, D1 provides solutions to the problem identified in the above mentioned single general concept. Therefore, the single general concept which could link the different inventions of the present application cannot be considered as inventive and there is a lack of unity.

IV.4. In the light of the above, six inventions have been identified (see Form PCT/ISA/210 for details).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D2: US-A-3 301 869 (LUNSFORD CARL D) 31 January 1967 (1967-01-31)
D3: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OGINO, YOSHIO ET AL: 'Preparation of 2-aryl-2-

hydroxyacetic acid ester derivatives as muscarinic M3 receptor antagonists' retrieved from STN Database accession no. 136:118468 XP002222161 & WO 02 004402 A (BANYU PHARMACEUTICAL CO., LTD., JAPAN) 17 January 2002 (2002-01-17) -& EP 1 302 458 A (BANYU PHARMA CO LTD) 16 April 2003 (2003-04-16)

D4: FR-A-2 155 927 (SYNTHELABO) 25 May 1973 (1973-05-25)

D5: EP-A-0 863 141 (BANYU PHARMA CO LTD) 9 September 1998 (1998-09-09)

D6: US-A-3 714 357 (GUEREMY C ET AL) 30 January 1973 (1973-01-30)

D7: WO 01 04118 A (ALMIRALL PRODESFARMA SA ;BUIL ALBERO MARIA ANTONIA (ES); FERNANDEZ) 18 January 2001 (2001-01-18)

D8: FRANKO B V ET AL: 'DERIVATIVES OF 3-PYRROLIDINOLS-III. THE CHEMISTRY, PHARMACOLOGY, AND TOXICOLOGY OF SOME N-SUBSTITUTED-3-PYRROLIDYL ALPHA-SUBSTITUTED PHENYLACETATES' JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 2, no. 5, 1960, pages 523-540, XP008021298

D9: PATENT ABSTRACTS OF JAPAN vol. 005, no. 148 (C-072), 18 September 1981 (1981-09-18) -& JP 56 079688 A (OTA SEIYAKU KK), 30 June 1981 (1981-06-30)

V.1. Novelty:

Document D7, which is considered to represent the most relevant state of the art, discloses (cf. claim 1, 34,35) muscarinic receptor antagonists which may be used for the treatment of respiratory, urinary or gastrointestinal diseases and which differ from the subject-matter of the present application in that a quinuclidine represents the central nitrogen-containing ring, whereas in the present formula (I) it is a pyrrolidine ring.

Therefore, the **subject matter of present claims 1-33 is considered novel (Article 33(2) PCT)** over the prior art.

V.2. Inventive Step:

The problem to be solved by the present invention may therefore be regarded as the provision of further compounds for the treatment of respiratory, gastrointestinal, and urological disorders.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

Documents D1, D2, D3, D4, and D8 discloses compounds, similar to the compounds of present formula (I), which are inhibitors of gastrointestinal motility, muscarinic receptor antagonists, or useful for the treatment of gastric ulcer and which all contain the central pyrrolidine ring. Therefore, it would have been obvious to the skilled person to combine the teaching of D7 with the one of D1-D4 and D8, thus arriving at the presently claimed compounds.

Furthermore, in D1-D4, and D8 the present substituent B represents phenyl and in D5 B represents heteroaromatic groups such as furan, pyridine, thiophene.
In D1-D9 the group D corresponds to substituent (i) and in D6-D9 to substituent (ii).
Consequently, many compounds falling within the scope of present general formula (I) must be regarded as a combination of chemical entities disclosed in compounds known for their activity as muscarinic receptor antagonists, or for the treatment of gastrointestinal disorders.

Claims 21-25, relating to processes for the preparation of compounds according to formula (I) as well as their intermediates, can only be considered as involving an inventive step (Article 33(3) PCT) if the compounds of claim 1 are new and inventive.

Consequently, the subject matter of the present application cannot be considered as involving an inventive step (Article 33(3) PCT).

V.3. Industrial Applicability:
The present application relates to compounds which are useful for the treatment of respiratory, gastrointestinal, and urological disorders and the **subject matter of claims 1-29,32,33 is therefore considered as industrially applicable (Article 33(4) PCT).**